Claim 30 (amended). A medicament comprising at least one halogenated xanthene as a primary active component, wherein such medicament is for chemotherapeutic treatment of diseases of human and animal tissue.

REMARKS

Applicants have made minor amendments to Claims 1, 10, 13, 19 and 30 to correct certain irregularities in the language of the claims. Such amendments are not Festo-type narrowing amendments.

Applicants will now address each of the Examiner's rejections in the order in which they appear in the Office Action

1. Claims Rejections - 35 U.S.C. §102

A. Rejection over Goers et al.

The Examiner rejects Claims 1, 3-8, 19, 21-26 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Goers. This rejection is respectfully traversed.

In the Office Action, the Examiner alleges that Goers discloses the use of photosensitizers, which include "xanthences and in particular Rose Bengal, as therapeutic agents." The claimed invention of the present application, however, is patentably distinct from any alleged disclosure in Goers for at least the reasons outlined below.

(1) Goers requires conjugate agents; the claimed invention does not.

Dependent Claims 5-6 and 23-24 of the present application are directed to alternate embodiments of the present invention that make use of, among other means, conjugation of a halogenated xanthene to a chemical or biological targeting moiety. Their respective independent claims (i.e., Claims 1 and 19) require no such conjugation, and thus cannot be anticipated by Goers (which requires conjugate agents). Independent Claims 31 and 32, along with dependent Claim 33, entail no such conjugation whatsoever. Hence, the agents of independent Claims 1, 19, 31 and 32 are clearly an improvement on what is disclosed in Goers.

More specifically, in the present application, such conjugation is taught only as a way to further improve the already favorable pharmacokinetic properties of the halogenated xanthenes, as described by the following passages:

> "[0031] As an example of these desirable chemical, biochemical, and physical properties, the inventors have found that the prototypical halogenated xanthene, Rose Bengal, will accumulate preferentially in (*e.g.*, target) some tumors and other tissues and pathogenic entities and exhibit high cytotoxicity within such tumors, tissues and pathogenic entities, while exhibiting negligible systemic cytotoxicity or local cytotoxicity in surrounding healthy tissues. Such agents also possess the ability to clear rapidly from healthy tissue in the body."
>
> "[0045] Moreover, the facility with which the halogenated xanthenes target specific tissues or other sites *can be further optimized* by attachment of specific functional derivatives at positions R^1 and R^2, so as to change the chemical partitioning and/ or biological activity of the agent. For example, attachment of one targeting moiety or more at positions R^1 or R^2 can be used to improve targeting to specific tissues, such as cancerous tumor tissues or sites of localized infection. An example of this is esterification at position R^1 with a short aliphatic alcohol, such as *n*-hexanol, to produce a derivatized

agent exhibiting enhanced partitioning into lipid-rich tumor tissues." (emphasis added)

The first passage teaches that the halogenated xanthenes are useful, as for example claimed in independent Claims 1 and 19, in their native (i.e., non-conjugated) form, affording preferential accumulation in target tissues, rapid clearance from healthy tissues, and high cytotoxicity within certain tumors. It is only as an additional refinement, that conjugation is taught, as illustrated by the second passage. In contrast, Goers fails to teach any such non-conjugated use of any halogenated xanthene, and instead teaches away from such use.

In particular, Goers teaches that "photochemicals" (including in this class, per the table at col. 20, lines 50-55, photosensitizers such as Rose Bengal) do not offer sufficient intrinsic targeting to be clinically useful. The background of the invention in Goers paints the following perspective on such agents:

> "Despite promising developments ... photochemicals (e.g., hematoporphyrin and other *photosensitizers*) *have several disadvantages* for clinical use. First, there is *great potential for damage to normal tissue*.... A second disadvantage is that patients receiving photoradiation therapy are generally *extremely sensitive to sunlight* .... Third, the dosage levels of photosensitizer required for therapy are very high and may have a *negative effect on normal tissue*.
>
> "The ideal photosensitizer should be designed so that it has greater tumor specificity, requiring a lower therapeutic dose level, hence mitigating the deleterious effect of higher doses. Greater tumor specificity leads to more efficient localization to the site of action and less opportunity for dispersal throughout the body.
>
> "Mew et al. have demonstrated the use of monoclonal antibody conjugated ... to hematoporphyrin as an anti-cancer agent in vivo and in vitro (1983, J. Immunol. 130:1473-1477)." (col. 6, lines 9-31, emphasis added)

Thus, Goers characterizes photosensitizers as intrinsically dangerous (i.e., resulting in damage to normal tissue, eliciting prolonged photosensitivity, and incurring "a negative effect on normal tissue"). The reference also describes a need to improve photosensitizers' targeting (i.e., "the ideal photosensitizer [would afford] greater tumor specificity"), and provides a road map for achieving such specificity (i.e., "Mew et al. have demonstrated [the advantages of linking photosensitizers to antibodies]"). Such teachings contradict those of the present invention concerning the intrinsic safety and targeting of the claimed medicaments (which are substantially comprised of, for example, non-conjugated Rose Bengal).

That Goers fails to disclose and actually teaches away from any such non-conjugated use of the halogenated xanthenes (or any other non-conjugated "photochemical" or photosensitizer) is made clear throughout the specification in Goers', such as in the field of invention:

> "The present invention relates to the general area of antibody systems capable of delivering therapeutic agents to target sites in vivo. The *therapeutic agents are covalently attached to antibodies or antibody fragments* either through linkers or by direct attachment to form antibody conjugates. The antibody-therapeutic agent conjugates substantially retain the immunospecificity and immunoreactivity of the original antibody." (col. 3, lines 6-13, emphasis added)

This passage unambiguously teaches that therapeutic agents are targeted to the desired tissues using antibodies or antibody fragments covalently attached (i.e., chemically bound) to such therapeutic agents. This fundamental theme is reinforced by Goers' summary of invention:

> "According to the general method of the present invention, a therapeutic agent is covalently attached to an antibody or antibody fragment....
>
> "In particular, the invention concerns methods for preparing antibody-therapeutic agent conjugates, comprising:

> "(a) reacting an antibody or antibody fragment with an oxidizing agent to form an aldehyde group in the carbohydrate moiety of the antibody or antibody fragment;
>
> "(b) reacting the aldehyde group of the resultant oxidized antibody or antibody fragment with an amine group of a linker ... to form an antibody-linker intermediate having substantially the same immunoreactivity and immunospecificity as the unconjugated antibody or antibody fragment; and
>
> "(c) covalently attaching the linker portion of the antibody-linker intermediate to a therapeutic agent to form an antibody-therapeutic agent conjugate." (col. 6, lines 34-61)

Thus, in keeping with its prejudice against native, non-conjugated therapeutic agents, Goers teachings are confined to conjugate agents (and more specifically, antibody-conjugate agents).

Even in an alternate embodiment, Goers expresses interest solely in such conjugate agents, as evidenced, for example, by the following passage:

> "In certain circumstances, it may be desirable to separate the above-described method for preparing antibody-therapeutic agent conjugates into two parts. The first part would produce an antibody-linker intermediate which may be considered a step in the production of the final antibody-therapeutic agent conjugate. Such antibody-linker intermediates may be stored for later combination with the particular therapeutic agent. Thus, the first part of the two part method would involve steps (a) and (b) above to form the intermediate antibody-linker intermediate. The second part, possibly at a later point in time, would involve covalently attaching the linker portion of the antibody-linker intermediate to a therapeutic agent to *produce the final antibody-therapeutic agent conjugate.*" (col. 6, line 62 - col. 7, line 8, emphasis added)

Here, Goers makes it unambiguous that the invention disclosed therein includes antibody-conjugate agents, even if such agents are produced using multiple steps.

Goers also makes it clear that such conjugate agents (and not any of their sub-components) comprise the entire invention, and are the basis for any therapeutic use of that invention:

> "The antibody-therapeutic agent conjugates of the invention are ideally suited for in vivo therapy. *Delivery of therapeutic agents* to specific target sites involves *administering* to an animal or human *an effective amount of an antibody-therapeutic agent conjugate*, wherein said antibody-therapeutic agent conjugate is immunoreactive with and immunospecific for an antigenic determinant of said specific tissue and substantially non-immunoreactive with and non-immunospecific for nonspecific tissue and said antigenic determinant is not found in substantial amount in non-specific tissue." (col. 12, lines 45-56, emphasis added)

This very focused disclosure culminates in Goers' description of the invention, "in its most general" form:

> "In its most general concept, *the invention contemplates site selective attachment of therapeutic agents to those areas of antibodies or antibody fragments* which are not a part of nor directly involved with the antigenic site of the molecule. Thus, after selective attachment to one of these sites (located outside the antigen binding region), the antibody conjugate formed has substantially the same immunoreactivity and immunospecificity as the unconjugated antibody or antibody fragment." (col. 13, lines 1-10, emphasis added)

In contrast to these teachings of Goers, which *require conjugation of a therapeutic moiety, such as Rose Bengal, to an antibody or antibody fragment*, the present application (1) not only teaches that such *conjugation is an optional, unnecessary refinement* of a more fundamental claimed invention (i.e., the halogenated xanthenes may be used successfully without conjugation), but (2) the present application further teaches that, if such conjugation methods are utilized, the general approach of the present invention is *far broader* and an improvement on that taught by Goers (i.e., conjugation of the halogenated xanthenes to other targeting moieties, such as esterification with a short aliphatic alcohol, as described supra, is useful for enhancing disease-specific targeting).

For at least these reasons, the extremely narrow teachings in Goers (i.e., comprising an antibody conjugated to Rose Bengal) cannot anticipate the subject matter of the independent claims

of present application (which does not require antibody conjunction to Rose Bengal or other halogenated xanthenes).

(2) Goers requires photosensitization; the claimed invention does not.

While Goers discloses a use of Rose Bengal (for example, as noted by the Examiner, at col. 20, lines 50-55 of Goers), this is not the same as the present invention. For example, Goers' description of "photoradiation therapy" (i.e., col. 28, lines 45-68) does not disclose any chemotherapeutic use of the halogenated xanthenes as claimed in the present application. Rather, this passage, taken together with the other passages cited by the Examiner, show that certain embodiments in Goers' together comprise:

a) a photosensitizer attached to an antibody to form a photosensitizer-antibody conjugate agent;

b) delivery of such conjugate agent to diseased tissue; and

c) subsequent photoactivation of such conjugate agent using applied optical radiation (i.e., light).

Thus, in addition to the aforementioned requirement concerning use of a conjugate agent, Goers further teaches away from the fundamental subject matter of the present application (and each of its pending independent claims) by requiring photoactivation of his conjugate agents. Any doubt that Rose Bengal is, as defined by Goers, solely a photosensitizer is dispelled by the following:

> "According to one embodiment of the present invention, photochemicals including photosensitizers ... may be used as therapeutic agents. Efficient photosensitizers include, but are not limited to ... rose bengal ...." (col. 20, lines 48-55)

Goers' use of photosensitizers (such as Rose Bengal) for photosensitization requires the use of light for their activation:

> "According to another method of the present invention, a photosensitizer is attached to an antibody carrier molecule .... *After delivery* of the antibody conjugate to the target site, *the photosensitizer is activiated* [sic] *by light* of the appropriate wavelength and its cytolytic effects on nearby cells are mediated through the generation of singlet oxygen molecules and oxygen free radicals." (col. 13, lines 36-44, emphasis added)

Since the therapeutic agents of the claimed invention require neither (a) conjugation to an antibody in order to function properly, nor (b) activation using light energy after delivery to their target tissue, the teachings in Goers are contrary to those of the claimed invention and cannot, therefore anticipate such invention.

Therefore, for at least the above-stated reasons, the rejected claims are clearly not disclosed or suggested by Goers but are patentable thereover. Hence, it is respectfully requested that this rejection be withdrawn.

B. Rejection Over Bottiroli

The Examiner also rejects Claims 1-11, 19-27 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Bottiroli et al. This rejection is also respectfully traversed for at least the reasons discussed below.

(1) Bottiroli requires conjugate agents; the claimed invention does not.

Similar to that discussed supra with respect to Goers, Bottiroli requires the use of conjugate agents, as illustrated by the following passages from the reference:

"Fluorogenic substrates in the present invention are *derivates of xanthenes ... containing quencher groups* such as for example the acetate, sulphate, phosphate, dibutyryl ester, galacto-pyranoside, glucoronide, acetamide-dioxyglucopyranoside groups, respectively *recognisable by the enzymes*: esterase, sulphatase, phosphatase, lipase, beta-galactosidase, beta-glucoronidase, and glucoso-aminidase.

"These quencher groups have the characteristic of *suppressing* the properties of fluorescence and the *photosensitisation activity* of the molecules in which they are introduced, and of being removed by the specific enzyme activity, preferentially present in the tumour cells, when the substance has been incorporated in the cells.

"Thus *the quencher groups transform an active substance into an inactive substance* while the enzyme activity restores the active substance. The above-mentioned substrates can be used with advantage in the diagnosis and photodynamic therapy of tumours.

"Information is reported below about experiments performed using as fluorogenic substrate *Rose Bengal acetate*, which belongs to *the group of xanthene derivatives*.

"Similar results, however, have been obtained with a significant number of the substrates mentioned above." (p. 3, line 22 - p. 4, line 7, emphasis added)

This passage makes it clear that Bottiroli is exclusively concerned with conjugate agents, such as the cited example of Rose Bengal acetate. Such conjugate agents are even more tightly defined as those *containing quencher groups* that are *capable of being cleaved by specific enzymes* (i.e, esterase, sulphatase, phosphatase, lipase, beta-galactosidase, beta-glucoronidase, and glucoso-aminidase).

In contrast, as described in detail supra viz-a-viz Goers, dependent Claims 5-6 and 23-24, as filed, describe alternate embodiments of the present invention that make use of, among other things, conjugation of a halogenated xanthene to a chemical or biological targeting moiety. Their respective independent claims (i.e., Claims 1 and 19), *require no such conjugation*, and thus cannot be anticipated by Bottiroli. Furthermore, independent Claims 31 and 32, along with dependent

Claim 33, entail no such conjugation whatsoever. Instead, such conjugation is taught only as a way to further improve the already favorable pharmacokinetic properties of the halogenated xanthenes. Thus, while Bottiroli requires conjugation, the invention of the independent claims bears no such requirement, and accordingly Bottiroli cannot anticipate such invention.

Further, in the example passage from Bottiroli cited supra, the reference teaches that, by forming the disclosed conjugate agents, the reference makes such agents inactive (i.e., quenched). In contrast, the present application teaches that both the native (i.e., non-conjugate) and conjugate forms of Rose Bengal are therapeutically active. These latter teachings are exemplified, for example, by the following passage from the application:

> "[0031] ... the inventors have found that the prototypical halogenated xanthene, Rose Bengal, will accumulate preferentially in (*e.g.*, target) some tumors and other tissues and pathogenic entities and exhibit high cytotoxicity within such tumors, tissues and pathogenic entities, while exhibiting negligible systemic cytotoxicity or local cytotoxicity in surrounding healthy tissues."

Thus, the present application teaches and claims that the native form of Rose Bengal exhibits useful chemotherapeutic properties. Moreover, these therapeutic properties are substantially unaffected by derivatization (i.e., formation of a conjugate form), as evidenced by the following passages from the present application:

> "[0027] Selected properties (such as chemical constituents at positions X, Y, and Z and functionalities R^1 and R^2) of representative halogenated xanthenes are summarized in attached Table 1.... In general, the halogenated xanthenes are characterized ... *chemical and physical properties that are substantially unaffected by* the local chemical environment or by the *attachment of functional derivatives at positions R^1 and R^2.*" (emphasis added)
>
> "[0045] Moreover, the facility with which the halogenated xanthenes target specific tissues or other sites can be further optimized by

attachment of specific functional derivatives at positions R^1 and R^2, so as to change the chemical partitioning and/ or biological activity of the agent. For example, attachment of one targeting moiety or more at positions R^1 or R^2 can be used to improve targeting to specific tissues, such as cancerous tumor tissues or sites of localized infection."

Hence, whereas Bottiroli teaches that formation of a conjugate agent negatively affects the photochemical functioning of Rose Bengal (i.e., "suppressing ... photosensitisation activity"), the present application teaches that conjugate forms do not lose chemotherapeutic function. Applicants respectfully submit that such diametrically opposed teachings cannot anticipate.

(2) Bottiroli requires photosensitization; the claimed invention does not.

While Bottiroli discloses use of certain derivatives of Rose Bengal, this is not the same as the claimed invention. For example, Bottiroli's description of "photosensitization" does not disclose any chemotherapeutic use of the halogenated xanthenes as claimed in the present application. More particularly, Bottiroli states:

> "We have now found fluorogenic substrates susceptible of... photosensitisation by enzyme transformation, which make it possible to obtain improved and unforeseen results in the ... photodynamic treatment of tumours.
>
> "These substrates consist of fluorescent substances with photosensitisation activity chemically modified with a group that quenches the properties of fluorescence and photosensitisation activity, this quencher group being removable by the specific enzyme activity, preferentially present in the tumour cells, with restoration of the properties of ... photosensitisation activity of the original substance." (p. 2, lines 24-31)

Thus, this passage, taken together with the other passages cited by the Examiner, show that the invention of Bottiroli contains:

a) attachment of a photosensitizer to a quencher group to form a photosensitizer-quencher conjugate agent (that is inactive until cleaved by certain enzymes);

b) delivery of such conjugate agent to diseased tissue;

c) enzymatic cleavage of such conjugate agent within such diseased tissue; and

d) subsequent photoactivation of such cleaved conjugate agent using applied optical radiation (i.e., light).

Thus, in addition to the aforementioned requirement concerning use of a conjugate agent, Bottiroli further teaches away from the fundamental subject matter of the present application (and each of its pending independent claims) by requiring the step of photoactivation of the conjugate agent. Any possible doubt that Rose Bengal functions, as defined by Bottiroli, solely as a photosensitizer is dispelled by the following passage from Bottiroli:

> "... cells treated with Rose Bengal or with Rose Bengal acetate ... were submitted to irradiation at 540 ± 5 nm by a Xe 75 W lamp and an interference filter.
>
> "Irradiation was realised with a power of 2 mw/cm^2 for various times until the administration of a maximum dose of 2.4 J, in accordance with the protocols normally used in tests of phototoxicity.... The *expression of phototoxicity* was defined as the ratio between the number of cells present after the treatment and those counted on the untreated controls. FIG. 5 shows the cell survival curves so calculated, evidencing a *strong phototoxic effect* in the case of treatment with Rose Bengal acetate (curve (a)) as compared with Rose Bengal (curve (b)). This effect relates directly to the quantity of fluorescent substance with photosensitisation activity produced by the enzyme activity, evaluated as fluorescence intensity at 580 nm (FIG. 4)." (p. 7, line 21- p. 8, line 2, emphasis added)

This passage makes it clear that the teachings in Bottiroli concern, solely, certain forms of Rose Bengal that are made to become therapeutic (i.e., to evidence a "strong phototoxic effect") only

upon irradiation with light. In fact, Bottiroli indicates that the agents disclosed therein are not therapeutically active without such irradiation, for example, by the following:

> "Tests of cellular vitality ... have shown that with incubation for 4 h at concentrations up to $1x10^{-4}$ M there is no significant cell mortality for Rose Bengal acetate or for Rose Bengal. The finding relative to Rose Bengal agrees with the literature (R. P. G. Feenstra and S. C. G. Tseng, Ophthalmology, 99 605, 1992)." (p. 7, lines 16-20)

Bottiroli herein reports that, in the absence of photoactivation (i.e., in the absence of irradiation with light), "no significant cell mortality" occurs. Bottiroli thereby teaches away from the fundamental teachings of the claimed invention and present application, which itself shows that desirable, selective cell mortality can be produced using chemotherapeutic agents comprised substantially, for example, of Rose Bengal, without the requirement of additional light activation.

(3) Bottiroli fails to observe or predict any chemotherapeutic properties of Rose Bengal.

The fact that Bottiroli fails to observe or predict any chemotherapeutic properties of Rose Bengal (as evidenced, for example, by the data on cellular vitality at p. 7, lines 16-20 of Bottiroli, cited supra) illustrates the novelty of the claimed invention, which is supported by e.g. Figure 3 of the present application. Bottiroli's tests of cellular vitality were conducted at a concentration of $1x10^{-4}$ M Rose Bengal (i.e., 0.1 mg/mL). Applicants discovered, as shown in the data of Figure 3, that such concentration is at the threshold for onset of cytotoxicity for this compound. Bottiroli, however, fails to observe or predict any chemotherapeutic properties of Rose Bengal (or any other halogenated xanthene), thereby completely missing their potential use as chemotherapeutic agents, as claimed in the present application.

Since the therapeutic agents of the claimed invention require neither (a) conjugation to an enzyme-cleavable quencher in order to function properly, nor (b) activation using light energy after delivery to their target tissue, the teachings in Bottiroli are contrary to those of the claimed invention and cannot, therefore anticipate such invention.

For at least the aforementioned reasons, Applicants respectfully submit that the rejected claims of the present application are clearly distinguishable and patentable over Bottiroli and should be allowed. Accordingly, it is requested that this rejection now be withdrawn.

C. Rejection Over Schultz

The Examiner also rejects claims 1, 3-6, 19, 21-24 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Schultz et al. This rejection is also respectfully traversed for at least the following reasons.

(1) Schultz requires conjugate agents; the claimed invention does not.

Similar to that discussed supra with respect to Goers and Bottiroli, Schultz requires the use of conjugate agents, as illustrated by the abstract therein:

> "*Polypeptide compositions* are provided having a binding site specific for a particular target ligand and further *having an active functionality* proximate the binding site. The *active functionality may be a reporter molecule* .... Alternatively, the *active functionality may be a chemotherapeutic agent*, in which case the polypeptide compositions are useful for therapeutic treatment of various diseased states." (emphasis added)

Thus, Schultz's compositions are conjugate compositions (containing either diagnostic or therapeutic agents, depending upon the type of "active functionality" attached to the polypeptide).

In contrast, the present application teaches that the native form of Rose Bengal exhibits useful chemotherapeutic properties. Moreover, these therapeutic properties are substantially unaffected by derivatization (i.e., formation of a conjugate form). Since the invention of the independent claims is free of the limitations of Schultz, Schultz cannot anticipate the claimed invention.

(2) Schultz does not teach a therapeutic use of Rose Bengal or any halogenated xanthene.

Schultz describes two categories of conjugated polypeptides, namely diagnostic conjugate agents and therapeutic conjugate agents. This is clear from the Description of the Specific Embodiments in Schultz, which states:

> "Novel polypeptides having binding sites capable of specifically binding a predetermined target ligand include at least one active functionality proximate the binding site.... *The active functionality may be a reporter molecule*, whereby the polypeptides will be *useful in detecting* the predetermined target ligand in a sample suspected of containing such ligand.... *Alternatively, the active functionality may be a chemotherapeutic agent*, whereby the polypeptide will be *useful in treating a diseased state* by site-specific drug delivery. Localization of the drug proximate the binding site will increase the efficiency of drug delivery by reducing the total drug dosage required. Side effects of the drug related to non-specific delivery will also be reduced." (col. 4, line 58 - col. 5, line 10, emphasis added)

Thus, Schultz's reporter-molecule conjugate is used for diagnostics (i.e., "detecting the predetermined target ligand in a sample") while the chemotherapeutic-molecule conjugate is used for treating a disease state. The respective identities of such classes are established by several passages therein, including the following:

> "*Reporter molecules* and compounds are selected to *provide a detectable signal .... Suitable reporter molecules include* chromogens (e.g., dyes and *fluorophores*)....
>
> "A wide variety of fluorescers may be employed either by themselves or in conjunction with quencher molecules. *Fluorescers of interest* fall into a variety of categories having certain primary functionalities. These primary functionalities *include ... xanthene....*
>
> "*Individual fluorescent compounds* which have functionalities for linking or which can be modified to incorporate such functionalities *include ... rose bengal....*" (col. 9, line 32 - col. 10, line 27, emphasis added)

In this passage, Schultz teaches that the xanthenes comprise one of several classes of "fluorescers of interest," and Rose Bengal is listed as a specific fluorescent compound of interest. Thus, Schulz teaches that xanthenes and Rose Bengal have a diagnostic use (i.e., as diagnostic reporter molecules useful with his conjugate polypeptides).

Turning to Schultz's separate class of chemotherapeutic agents, the reference teaches the following:

> "Chemotherapeutic agents will be selected depending on the diseased state which is being treated as well as on the nature of the target ligand. Such agents may be intended to kill diseased cells of the host, kill pathogens, inhibit cellular proliferation, provide hormone therapy, or provide a wide variety of other beneficial interactions between the agent and the target ligand. Exemplary chemotherapeutic agents include toxins, toxin fragments, bactericides, radical scavengers, radical generators, alkylating agents, neurotransmitters, radionuclides, antiviral compounds, antifungal compounds, antineoplastic agents, antimycoplasmal agents, heavy metals, and the like. A list of suitable drugs is provided in Table 1. (col. 11, lines 8-21)

In contrast to the aforementioned case for "reporter molecules," Schultz fails to include xanthenes or Rose Bengal in this list of chemotherapeutic agents (this is also the case for Table 1 in

the reference). Accordingly, Schultz fails to disclose or suggest any chemotherapeutic role for the xanthenes or Rose Bengal.

The fact that Schultz lists xanthenes and Rose Bengal as useful diagnostic agents yet fails to disclose a chemotherapeutic use for such xanthenes or Rose Bengal is consistent with what Applicants believe to be a general opinion among those of skill in the art, namely that such compounds are non-toxic (see, for example, Bottiroli's reference to the prior art of Feenstra and Tseng, discussed supra). Due to this prevailing opinion, it would be illogical for Schultz to list the xanthenes and Rose Bengal as potential chemotherapeutic agents (especially short of some unanticipated result).

In contrast to these orthodox teachings of Schultz, Applicants discovered the novel concept of the present application: that Rose Bengal, for example, can be non-toxic at low concentrations, but under certain conditions, such as when used at higher concentrations, it can be quite toxic. Moreover, the present application teaches how to make such toxic properties therapeutically useful (i.e., for chemotherapy). Since Schultz fails to show or predict such chemotherapeutic uses, this reference does not disclose or suggest the claimed invention and cannot anticipate it.

Therefore, for at least the above-stated reasons, it is respectfully submitted that Schultz fails to disclose or suggest the claimed invention, and that the claims of the present application are patentable thereover. Accordingly, it is requested that this rejection be withdrawn.

Therefore, for at least the above-stated reasons, it is respectfully requested that each of the §102 rejections be withdrawn.

II. Claim Rejections - 35 U.S.C. §103

The Examiner also rejects claims 2 and 20 under 35 U.S.C. §103(a) as being obvious over Goers et al. This rejection is also respectfully traversed for at least the following reasons.

(1) Goers requires conjugate agents; the claimed invention does not.

As discussed in detail supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of conjugate agents. In contrast, the claimed invention does not require such conjugation. For at least this reason, the teachings in Goers does not render the claimed invention obvious.

(2) Goers requires photosensitization; the claimed invention does not.

Also as discussed in detail supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of photosensitization with its conjugate agents. In contrast, the claimed invention does not require such photosensitization. For at least this reason, the teachings of Goers does not render the claimed invention obvious over Goers.

Since the therapeutic agents of the claimed invention require neither (a) conjugation to an antibody in order to function properly, nor (b) activation using light energy applied after delivery to their target tissue, and since both such features are required by Goers, the teachings in Goers are contrary to those of the claimed invention and cannot, therefore make the invention in part or as a whole obvious.

Therefore, for at least the reasons discussed above, it is respectfully requested that the §103 rejection be withdrawn.

III. Double Patenting

The Examiner also rejects Claims 1-11, 19-27 and 31-33 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-10, 12-19, 21-30, 32-34 and 36-38 of co-pending application no. 09/635,276 and Claims 1-44 of co-pending application no. 09/799,785. These rejections are respectfully traversed.

However, in order to advance the prosecution of this application, Applicants are submitting herewith two terminal disclaimers to overcome the double patenting rejections. Accordingly, it is requested that these rejections be withdrawn.

IV. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this response, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: May 7, 2003

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Marked-up copy of the amendments made herein:

IN THE CLAIMS:

Please amend the claims as follows:

Claim 1 (amended). A medicament comprising at least one halogenated xanthene as a primary active component, wherein said medicament is [useful] for chemotherapeutic treatment of diseases of human and animal tissue.

Claim 10 (amended). The medicament of Claim 1 wherein said medicament is [useful] for the treatment of indications selected from the group consisting of diseases of [conditions affecting] the skin and related organs, diseases of [conditions affecting] the mouth and digestive tract and related organs, diseases of [conditions affecting] the urinary and reproductive tracts and related organs, diseases of [conditions affecting] the respiratory tract and related organs, diseases of [conditions affecting] the circulatory system and related organs, diseases of [conditions affecting] the head and neck, diseases of [conditions affecting] the endocrine and lymphoreticular systems and related organs, diseases of [conditions affecting] connective tissues, diseases of [conditions affecting] tissue surfaces exposed during surgery, and diseases caused by [conditions related to] microbial, viral, fungal, and parasitic infection.

Claim 13 (amended). The use of Claim 12 for preparation of a medicament for the treatment of indications selected from the group consisting of diseases of [conditions affecting] the skin and related organs, diseases of [conditions affecting] the mouth and digestive tract and related organs, diseases of [conditions affecting] the urinary and reproductive tracts and related organs, diseases of

[conditions affecting] the respiratory tract and related organs, diseases of [conditions affecting] the circulatory system and related organs, diseases of [conditions affecting] the head and neck, diseases of [conditions affecting] the endocrine and lymphoreticular systems and related organs, diseases of [conditions affecting] connective tissues, diseases of [conditions affecting] tissue surfaces exposed during surgery, and diseases caused by [conditions related to] microbial, viral, fungal, and parasitic infection.

Claim 19 (amended). A chemotherapeutic pharmaceutical composition for intracorporeal administration comprising a halogenated xanthene [for chemotherapeutic treatment].

Claim 30 (amended). A medicament comprising at least one halogenated xanthene as a primary active component, wherein such medicament is [useful] for chemotherapeutic treatment [,] of diseases of human and animal tissue.